UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,851	02/01/2006	Jean-Marie Saint-Remy	50304/112001	9175

21559 7590 05/18/2009

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,851	SAINT-REMY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-65* is/are pending in the application.

4a) Of the above claim(s) *46 and 48-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-40,42-45,47 and 58-64* is/are rejected.

7)☒ Claim(s) *41 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/06, 10/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

DETAILED ACTION

1. Applicant's response and amendments received February 24, 2009 are acknowledged.

Claims 1-33 have been canceled.
Claims 41 and 43-45 have been amended.
Claims 58-65 have been added.
Claims 34-65 are pending in the instant application.
Claims 46 and 48-57 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the office action mailed January 25, 2008.

Applicant's election with traverse of the antibody species recited in newly presented claim 58 (90% similarity to SEQ ID NOs:2 and 4 with the glycosylation site from Asn47 to Thr49 being mutated in the reply filed on February 24, 2009 is acknowledged. The traversal is on the ground(s) that the species are entitled to unity of invention because Co et al. teach increasing the affinity of an antibody by modifying glycosylation whereas the instant antibodies have "substantially the same" affinity as the staring antibody. This is not found persuasive because of the reasons communicated to applicant in the December 24, 2008 office action. Specifically, "substantially the same" is not explicitly defined by the specification and thus reasonably includes increased, decreased and the same affinity as a starting antibody.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 34-45, 47, and 58-65 are under examination as they read on the elected species of antibody.

Information Disclosure Statement

3. The IDS forms received 2/1/06 and 10/14/08 are acknowledged and have been considered.

Specification

4. The title is objected to as not clearly indicating the subject matter that is claimed in the instant application. A new title that better reflects the claimed invention is suggested.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The hybridoma named Krix-1 is recited directly in claim 38 while derivatives of the antibody made by this hybridoma are recited in claim 40. Thus this material is a required element need to make the claimed invention. As a required element, this material must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent hybridoma. See 37 CFR 1.801-1.809 and MPEP 2401-2410.

It is noted that the hybridoma Krix-1 is disclosed as having been deposited under the terms of the Budapest treaty on page 39 of the instant specification. However, neither the conditions under which the deposit was made, nor assurances that the material will be replaced if it becomes unviable and that it will be irrevocably and unconditionally released to the public upon issuance of a patent in this application do not appear to be indicated in the instant specification.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit

or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that Krix-1 has deposited under the Budapest Treaty and that Krix-1 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer. See 37 CFR 1.806 and MPEP 2410-2410.01. If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the vector described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

7. Claims 34-40, 42-45, 47, and 58-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the antibody of SEQ ID NO:26, an antibody that binds FVIII and comprises the six CDRs of SEQ ID NOs:33-38 wherein the glycosylation site at positions 3 and/or 5 of SEQ ID NO:33 is mutated, an antibody that binds FVIII and comprises SEQ ID NO:4, an antibody that binds FVIII and comprises SEQ ID NO:2, and an antibody that binds FVIII and comprises SEQ ID NO:2 wherein SEQ ID NO:2 is mutated such that position 3 of CDR1 is mutated from N to Q,

E, or D or position 5 is mutated from T to A, does not reasonably provide enablement for more. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed a genus of antibodies which comprise "modified" glycosylation in the variable region as compared to a starting antibody which binds and inhibits the activity of factor VIII (a.k.a. an inhibitory antibody). This genus is further characterized in that the affinity of the modified antibody and the starting antibody are "substantially the same". The disclosure on page 22 indicates that to be "substantially the same", the K_D values should differ by less than a factor of 2.5. To support such a genus, applicant has disclosed working examples of antibody derivatives based upon KRIX-1, a known inhibitory antibody that binds FVIII in the C domain. KRIX-1 comprises a glycosylation site (i.e. Asn-Xaa-Ser/Thr) in CDR1 of the heavy chain, and the derivatives comprise mutations such that the Asn is replaced with Gln, Asp, Glu, or Ala. These derivatives are identified as Krix-1Q, Krix-1D, Krix-1E, and Krix-1A respectively.

The breadth of the independent claim reads on antibodies which comprise modified glycosylation, yet the staring antibody that is modified is not identified other than that it is an inhibitory antibody that binds FVIII. Note that while the working examples deal with the removal of glycosylation from Krix-1 via mutagenesis, the claims also read upon the introduction of a glycosylation site in the variable domain.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody

(Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

It is also known that given one specified variable domain, either heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Glycosylation within variable domains of antibodies is known in the art, yet the results of either introducing or removing such glycosylation upon antigen binding is not predictable. Indeed, introduction as well as removal of glycosylation in a CDR can either increase or decreased affinity for the cognate antigen, with the position where the N-glycan is attached as well as the structure of the antigen and starting antibody influencing observed properties in unpredictable ways (see particularly Wright et al., Endo et al., and US patent 5,714,350). Typically, reported changes in affinity are more than 3 fold. However, the specification indicates on pages 20-21 that the inventors' observations are unexpected because it has not been previously reported that glycosylation can modulate the function of an antibody other than by altering the antibody's affinity or specificity. Given the unexpected nature of applicant's observations, as well as the teachings of unpredictability in the art, a skilled artisan would not reasonably expect that use of a staring inhibitory antibody other than Krix-1, or the introduction of another glycosylation site into the variable domain of Krix-1 would generate an antibody that differs by less than a factor of 2.5 in its affinity for binding FVIII.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation, applicant's claimed genus of antibodies which recite "percent identity" or "sequence similarity" are not reasonably enabled because they read on mutations which can occur with the CDRs of the variable domain. As evidenced by the enclosed sequence alignment,

antibody sequences that are more than 90% similar can be found in the databases that are specific for antigens other than FVIII, indicating that additional structural information is needed to ensure maintenance of antigen specificity. Note that the working examples have designated two positions in CDR1 of the heavy chain which can be mutated (i.e. 3 or 5) yet claims such as 64 recite that the mutation can occur at positions 3, 4, or 5. Note also that in order to perform any sort of screening assay to identify other antibody chains (either heavy or light) a specifically defined antibody chain of a single sequence is needed to perform the screening assay as per Portolano et al. Thus, a claim such as 42 is not reasonably enabled because it allows for two variables (i.e. the heavy chain comprises unknown mutations and the light chain can be anything) yet screening assays used to identify such antibodies require one of the variables to be a constant.

Therefore, based upon the breadth of the claimed invention, the teachings of the art, and the amount of guidance and direction disclosed in the specification, a skilled artisan would be unable to make and use the full breadth of the claimed genus of antibodies without first performing additional, unpredictable research.

Claim Objections

8. Claims 41 and 65 are objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka/
Primary Examiner, Art Unit 1644